

Congenital disorder of glycosylation type II: Case report

CDG type 2

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Congenital disorder of glycosylation (CDG) is an inherited metabolic disease characterized by defects in the synthesis of glycan groups of glycoproteins and glycolipids.

In this study, we present the clinical, pathological and physical evaluation of a 10-year-old female patient who is still alive and has been diagnosed with CDG type 2, accompanied by musculoskeletal, heart, liver, lung involvement, vision and hearing problems, dysmorphic facial findings, as well as the affected central nerve system.

The necessary measures were taken considering all possibilities and the fact that she did not have a clear diagnosis at a very early age and was diagnosed after a comprehensive evaluation. In particular, the physical treatment process, which started at a very early age, substantially prevented the delayed musculoskeletal, respiratory and circulatory problems by extending over a period of time. In this context, we think that our case is rare in the literature.

Keywords

Congenital disorder of glycosylation (CDG); Metabolic disease; Pediatrics; Genetics

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Introduction

Congenital disorder of glycosylation (CDG) is an inherited metabolic disease characterized by defects in the synthesis of glycan groups of glycoproteins and glycolipids [1]. This disease was first described by Jaeken et al. in 1980 in Belgium as carbohydrate-deficient glycoprotein syndrome [2].

After translation, proteins are modified to asparagine in N-glycosylation by adding sugar groups through serine and threonine in O-glycosylation. Since N-glycosylation is a multi-step process, polyglycan is first synthesized on dolichol, then glycan is transmitted to protein in the endoplasmic reticulum, and the glycan on protein is modified in the Golgi apparatus. Damages involving the steps in the endoplasmic reticulum and the Golgi apparatus present as CDG type I. Enzymatic damages associated with glycan modification in the Golgi apparatus are defined as CDG type II [3].

Combined defects involve the coexistence of O- and N-glycosylation disorders. Recently, 25 enzymes, which deficiencies lead to different presentations, have been identified [4].

Common clinical and laboratory findings of CDG in the prenatal period include intrauterine growth retardation, congenital microcephaly, severe fetal hypokinesia, corpus callosum atrophy, Dandy-Walker malformation, and non-immune hydrops fetalis. Neurological findings include psychomotor growth retardation, microcephaly, progressive hydrocephalus, cerebellar hypoplasia, hypotonia, ataxia, stroke-like attacks, convulsion, and hearing loss. In the ophthalmologic examination, iris coloboma, cataract, pigmentary retinopathy, optic atrophy, strabismus, nystagmus may be observed, while gastrointestinal problems may be accompanied by recurrent vomiting, diarrhea, protein-losing enteropathy, Reye-like syndrome, hepatic fibrosis, hepatosplenomegaly and hypertransaminasemia. In dysmorphic evaluation, collapsed nipple, lipodystrophy, ichthyosis, lymphedema, skin hyperlaxity, joint hypermobility, joint deformity, bone dysplasias, nail deformities and non-specific dysmorphic findings may be observed. In addition to these findings, growth retardation, short stature, cardiomyopathy, pericardial effusion, heart failure, renal failure, nephrotic syndrome, unexplained fever attacks, immune deficiency, anemia, neutropenia, thrombocytopenia, reduced coagulation factors, elevated creatine kinase and hypothyroidism may be encountered [5].

Clinical findings as well as neurological findings and transferrin isoforms play an important role in the diagnosis of CDG. These disease findings can be confused with other diseases that are difficult to diagnose, and can mimic many diseases with neurological symptoms. Thus, conventional biochemical and molecular examinations as well as glycan analysis, enzyme activity and metabolite measurement should always be performed in the differential diagnosis of CDG [6,7]

In this study, we present the clinical, pathological and physical evaluation of a 10-year-old female patient who is still alive and has been diagnosed with CDG type 2 accompanied by musculoskeletal, heart, liver, lung involvement, vision and hearing problems, dysmorphic facial findings, as well as the affected central nerve system.

The necessary measures were taken considering all possibilities

and the fact that she did not have a clear diagnosis at a very early age and was diagnosed after a comprehensive evaluation. In particular, the physical treatment process, which started at a very early age, substantially prevented the delayed musculoskeletal, respiratory and circulatory problems by extending over a period of time. In this context, we think that our case is a rare case in the literature.

Case Report

The study was started after obtaining approval from the Inonu University Health Sciences, Non-Invasive Clinical Trials Ethics Committee in the 9th session dated 05.05.2020 (decision no. 2020/566). The family was informed about the content of the study and had signed the Informed Consent Form.

The girl patient, who was born to a 22-years old mother at 38 weeks of gestation by cesarean on 09/05/2009, was never actively breastfed, and for this reason the family applied to a hospital (Figure 1). Meanwhile, low saturation, hypoglycemia and fever were detected. Although the patient was discharged after receiving necessary treatment, family members repeatedly applied to the hospital with complaints of fever and cough, and the patient was given antibiotics. When she was 18 days old, she stayed in an incubator for one week. When she was 6 months old, she was followed up due to growth retardation and syndromic face. During this period, she was hospitalized due to respiratory distress. When she was 2.5 years old, she had 4-5 seizures per day and was given medication. When she was 4.5 years old, the frequency of seizures decreased up to 2 times per day from time to time.



Figure 1. Neonatal period

The result of the chromosome analysis performed on 11/11/2010 was found congruent with the genetic diagnosis of congenital glycosylation defect type 2a. The mother and father were children of aunts, and it was stated that definitive diagnosis will be made based on the result of the analysis of the samples from the family and retrospective clinical evaluation to further strengthen the relationship of these diagnosis variants with the disease.

When the file of the patient was examined retrospectively, the homozygote or compound heterozygote pathogenic variants in the Whole Exome Sequencing (WES) MGAT2 gene were found to be associated with an autosomal recessive congenital glycosylation defect type 2a based on the analysis with the next-generation sequencing method on 08/01/2018 (OMIM: 212066).

When examining the nerves and muscles of the lower extremity, based on the EMG result, a neurogenic lesion with sensory neuropathy, characterized by axonal degeneration and demyelination was determined.

The patient had a syndromic (dysmorphic) face, microcephaly, and deformity findings in wrists and elbows of the upper extremity and in knees, foot and ankles of the lower extremity. The highly arched palate and asymmetrical face findings were prominent and have worsened over time (Figure 2).



Figure 2. View of the patient's dysmorphic face type

The patient had functional scoliosis findings. In particular, valgus and eversion deformities of the ankle and foot lead to difficulty in walking.

Static and dynamic balance loss is occasionally observed. There is a general decrease in muscle strength. The patient gets tired

quickly and loses balance-coordination during exercise.

The patient has musculoskeletal problems, accompanied by mental retardation, speaking, respiratory, circulation, chewing and swallowing problems.

There are no medications that the patient has been taking regularly. In addition to special educational programs, she has received regular physical treatment and rehabilitation sessions, as well as swallowing, hearing and speaking.

The purpose of a physical treatment and rehabilitation program is to maintain respiratory capacity, prevent the development of deformity, increase muscle strength, improve gross and fine motor skills, improve balance and coordination and increase independence in daily living activities.

Discussion

The diagnosis of CDG types is closely associated with the individual-specific symptoms of the patient and long-term comprehensive evaluation [2].

The fact that the patient was kept under observation since the day she was born, her growth was evaluated thoroughly, she had a genetic susceptibility, as well as the fact that her mother and father were close relatives, suggested numerous metabolic diseases and eventually lead to making a definitive diagnosis. The majority of similar patients who were previously identified were diagnosed after they died [5].

The first CDG type 2b case reported by Preater et al. in 2000 was a girl baby who died at 2.5 months old. This case had generalized hypotonia, craniofacial dysmorphism, convulsion, feeding problems and hypoventilation findings, and our case had also similar findings [5].

In our country, Cansu et al., in 2005, reported a girl who had initially walking difficulties, musculoskeletal problems and atypical facial appearance and was diagnosed with CDG type 2 [6].

In 2008, they reported a girl patient with growth and development problems, as well as, dysmorphic face, liver involvement and mental retardation findings in 2008 [7].

The girl baby, who was hospitalized for the first time due to lung infection and neonatal cholestasis at the age of 2 months, was evaluated with suspicion of metabolic disease. The test results that did not congruent with any metabolic disease suggested that CDG as a provisional diagnosis, which was then confirmed by the result of the analysis of the serum sample sent abroad. However, the patient died on the day when the result became known. The patient died due to pneumonia. The prominent findings in the patient were hepatomegaly, dysmorphic face, highly arched palate, hand and foot deformities, joint contractures, pectus excavatum and scoliosis, which were also seen in our patients [2].

Recently, a 12-year-old female patient with a diagnosis of CDG type 2b, whose diagnosis was definitely made in the literature, has been reported. For CDG type 2b, this is a rare case, although it is clinically similar and different from our case [8].

Our case has a long life among previously identified types; however, the procedures applied to the patient since the day she was born were recorded, thereby providing very useful information for diagnosis and treatment.

Necessary measures were taken considering all possibilities

and the fact that she had no clear diagnosis at a very early age and was diagnosed after a comprehensive evaluation. In particular, the physical treatment process started at a very early age substantially prevented the delayed musculoskeletal, respiratory and circulatory problems by extending over a period of time. In this context, we think that our case is rare in the literature.

The number of identified cases has increased from past to present. This will be further increased, and further disease can be identified. In particular, CDG types should be suggested after the common findings in CDG types such as hypotonia, dysmorphic findings, mental retardation, seizures, musculoskeletal disorders, liver and heart involvement rule out other metabolic disorders.

Early diagnosis will allow the family undergo genetic screening and take measures for other children to be born. The development of different diagnosis methods for a disease that still has no cure may bring along treatment options.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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